**Title:** HIV screening performance using third generation enzyme linked immunosorbent assay compared to fourth-generation electrochemiluminescence immunoassay

**Author(s):** Jung Hee Chae, Kerrie Grunnet, Dan Laney, Taylor Phelps, Martin Steine, Se Yoo

1. Clinical Question: Should fourth-generation electrochemiluminescence immunoassay (ChIA) be used over third-generation enzyme linked immunosorbent assay (EIA) for HIV screening patients in multiethnic region of China?

PICO Parts:
- **P** – Patients tested for HIV during 2008-2011 in West China hospital in multiethnic region of China
- **I** – fourth-generation electrochemiluminescence immunoassay (ChIA)
- **C** – third generation enzyme linked immunosorbent assay (EIA)
- **O** – shifting from third to fourth generation HIV testing must be made with caution

   a. Database(s) searched: Ovid
   b. Keyword Search Terms used: electrochemiluminescence immunoassay
   c. MeSH Search Terms used: HIV infection, Mass screening, Diagnosis

3. Methods Description (setting, population, sample size, study design):
   The study was conducted from January 2008 to August 2011 at West China Hospital of Sichuan University. The patient population for this study was specimens retrospectively collected without any personal identifiers. This hospital serves a multiethnic region of China, thus specimens collected represent a heterogeneous population. To begin, 345,492 specimens were screened for the study. To be included in the study, the specimen must have been subjected to an HIV-1 test using either the third generation enzyme linked immunosorbent assay or the fourth generation electrochemiluminescence immunoassay. Results that could not be interrupted caused the specimen to be excluded from the study. Of the 345,492 initial specimens, 344,596 specimens had interpretable HIV test results. 1,112 specimens of the 229,286 tested with EIA had a positive test result. 769 of the 116,206 tested with ChIA presented a positive result. 596 of the EIA positive test results and 431 of the ChIA positive test results were subjected to confirmatory testing. This study, as described by the authors, is observational and we identified it as cross sectional study.

4. Methods Interpretation (Validity):
   a. Was there an independent “blind” comparison with a reference standard?
      No. The data used in this study was collected retrospectively without any identifiers. However because they used different samples collected during different time period as their data for comparison, it is difficult to say that a reference standard was strictly applied.
   b. Did the sample include an appropriate spectrum of patients to whom the diagnostic/screening test will be applied in clinical practice?
Yes. The data collected was from actual patients whom received routine HIV-screening tests under clinical settings.

c. Did the results of the diagnostic/screening test being evaluated influence the decision to perform the reference standard?
   Yes. As mentioned above, the two individual data collected for two assays compared were from different individuals. In addition, there was significant number of withdrawals over the course of the study.

d. Were the methods for performing the diagnostic/screening test described in sufficient detail to permit replication?
   Yes. The details were adequate regarding collection of data, assays (specific models used were included), confirmatory tests, and statistical analyses.

5. Results:
The results of this study were based on 344,596 specimens with interpretable HIV results. 228,761 of the specimens were tested with EIA, and the remaining 115,835 were tested with ChIA. Approximately 0.23% of the EIA-tested specimens were HIV-1 positive, and 0.26% of the ChIA-tested specimens were HIV-1 positive. The false positive rate of EIA (0.03%) (95% CI 0.02-0.04) was almost three times lower than that of ChIA (0.08%) (95% CI 0.06-0.10). Also, the positive predictive value of EIA (89.6%) (95% CI 87.1-92.1) was significantly higher than that of ChIA (76.1%) (95% CI 71.9-80.3). The clinical sensitivity of EIA was 99.64%, and for ChIA was 99.88%. Specimens tested with ChIA were noted to have more discordant results between the screening test and confirmation (via western blot). These results indicate that the fourth generation ChIA has higher sensitivity, but given its higher false positive rates, is not as specific as the third generation EIA test. The authors note a higher incidence of false positive results leads to misallocation of time and resources spent on follow-up testing. The cost-effectiveness of EIA is particularly important in developing countries, whose hospitals and clinics have limited resources and personnel devoted to HIV screening and diagnosis. The authors’ assessment of the advantages of EIA over ChIA are reasonable, given the demographic of patients being screened in China. However, the results of this study would be more compelling if the number of specimens tested with EIA and with ChIA were more alike, and also if the same specimens were tested with both assays. This would help to control for inherent variability of collected specimens, and provide a more direct comparison of EIA and ChIA.

6. Translational applications (How does this study apply to your patients?):
   · There is potential for this study to influence individual clinics decision to continue using the third generation (EIA) HIV test or convert to the fourth generation (ChIA) HIV test when screening for HIV while also taking into account that geographical and ethnic differences must be considered when choosing an HIV test.
   · The results have the potential to influence clinics to choose the EIA test over the ChIA test when screening patients due to its superior positive predictive value and specificity. Patients treated at clinics that choose EIA testing are at a reduced risk of experiencing the adverse effects resulting from a false positive HIV test, including but not limited to a decline in medical care due to inappropriate allocation of clinical resources.
   · We would recommend replicating the study in the US. There might be differences in the characteristics of the populations in the US and China. We recommend the study be replicated, this time testing the same sample of individuals within the same time period. We reiterate that geographical and ethnic differences must be considered when choosing between the HIV tests.

7. Reference: